

### REMARKS

Claims 1-18 are pending in the application. Favorable reconsideration in light of the Rule 132 Declaration and the remarks which follow is respectfully requested.

#### The Obviousness Rejection

Claims 1-18 stand rejected under 35 U.S.C. § 103(a) over Iwasaki et al (U.S. Patent 6,458,948). Iwasaki et al relates to carboxylic acid derivatives and generically describes compounds used to make such in Formula (I) in column 2. The Examiner notes that while Iwasaki et al does not exemplify the compounds of claims 1-18, Iwasaki et al generically describes equivalent compounds. The Examiner specifically contends that it would have been obvious to modify Iwasaki et al to have the same R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> groups as the claimed invention expecting the modified compounds to have the same use. Applicant respectfully disagrees.

One feature of the invention is that, as explicitly shown in claim 6, when making a carboxylic acid derivative from a carboxylic acid and a compound having a nucleophilic functional group, the compounds are dehydrated and condensed by mixing them in an aqueous solution in the presence of a compound represented by the formula I (formula I of claims 1 and 6). When making a carboxylic acid derivative, especially in the claimed method, the carboxylic acid and the compound having a nucleophilic functional group are both substrates for dehydrating condensation, and the compound represented by the formula I functions as a dehydrating condensing agent.

Since the dehydrating condensing agent of the claimed invention has at least one medium or long chain alkyl group in the quaternary ammonium structure, the dehydrating condensing agent is **amphiphilic**, and therefore the dehydrating condensing agent can advantageously form micelles in an aqueous solution, or the dehydrating condensing agent can be incorporated preferentially into micelles that are formed by another surfactant. In this case, for example, since the carboxylic acid

compound, which is the substrate, also has a hydrophobic moiety, the carboxylic acid compound can form micelles together with the dehydrating condensing agent, or the carboxylic acid compound can be incorporated preferentially into micelles that are formed by another surfactant.

As a result, at the water interface, both the condensation of the quaternary ammonium moiety of the dehydrating condensing agent of the claimed invention and the concentration of the carboxyl group of the carboxylic acid compound are much higher than those in the solution or the aggregation. Consequently, in the claimed invention, the carboxyl group is activated by addition of the triazino group to which the quaternary ammonium cation is bonded, thereby causing dehydrating condensation with the nucleophilic functional groups of the amine compounds or the alcohol compounds in the aqueous solution. This allows amide compounds or ester compounds to be generated more efficiently.

While Iwasaki et al discloses certain compounds useful as a dehydrating condensing agent for producing a carboxylic acid derivative from a carboxylic acid, the compounds described in Iwasaki et al are relatively **hydrophilic** and thus cannot form micelles. The reaction using the compounds of Iwasaki et al is therefore performed in a homogeneous system. As a result, the reactivity of the formula I compounds of the claimed invention is quite different from that of Iwasaki et al because the claimed compound forms **molecular aggregate phases such as micelles** and are therefore involved in efficient dehydrating condensations at a water interface (surface).

Generally speaking, the water interface is known as a field where a hydrolysis reaction is enhanced. For example, please see Jaeger and Ippoliti, *Journal of Organic Chemistry*, 1981, vol. 46, pp. 4964-4968 (hereinafter referred to as Jaeger); and Rico et al., *Journal of Organic Chemistry*, 1994, vol. 59, pp. 415-420 (hereinafter referred to as Rico); both of which were submitted via an IDS on November 3, 2006. In the abstract and footnote of page 4964 of Jaeger, page 417,

right column, second to third full paragraphs of Rico, and page 418, left column, second to third paragraphs of Rico, the authors describe that hydrolysis is enhanced in inverse micelle systems, and that dehydrating condensation is completely inhibited in the presence of a trace of water. Therefore, it would **NOT** have been obvious to those skilled in the art to perform a dehydrating condensation at an interface in inverse micelle systems where hydrolysis is enhanced but dehydrating condensation is ***inhibited***.

The inventor of the subject application has designed a cyclodextrin-based artificial enzyme in order to efficiently exert its catalytic activity as a dehydrating condensing agent which can be used in an aqueous solvent. Please see Kunishima et al., *J. Am. Chem. Soc.*, 2001, vol. 123, pp. 10760-10761 (hereinafter referred to as Kunishima), which was submitted via an IDS on August 8, 2006. In this case, the pseudo first order rate constant accelerates by a factor of 13, compared to cyclodextrin (Table 2 of Kunishima). As seen from Examples 4 and 5 of the present specification, the rate of the reaction under ***micelle formation*** is markedly increased to at least 100 to 1000 times faster than that of the monodisperse system. It would not have been expected that such a markedly faster rate would occur at the interface in an inverse micelle system where hydrolysis is enhanced but dehydrating condensation is inhibited. Thus, it is very difficult for those skilled in the art to predict that hydrolysis is enhanced in an inverse micelle system under a trace of water and thus furthermore difficult in a micelle system where a large amount of water is dispersed.

Although it is not conceded that the Examiner has established a *prima facie* case of obviousness, a Rule 132 Declaration is enclosed with this document to further rebut the obviousness rejection. The experiments in the attached Rule 132 Declaration demonstrate various effects on dehydrating condensation by using the claimed compounds.

The Rule 132 Declaration experiments demonstrate that increased lipophilicity of the carboxylate correlates to increase yield of the product (see Table 1 of the Rule 132 Declaration). This result is unexpected in view of the teachings of Iwasaki et al. The Rule 132 Declaration experiments further demonstrate that adding an organic solvent for purpose of firming an emulsion also accelerates the condensation reaction (see Table 2 of the Rule 132 Declaration). This result is likewise unexpected in view of the teachings of Iwasaki et al.

The Rule 132 Declaration experiments demonstrate that carbon chain length matters when calculating reaction efficiency with an amine (see Tables 3-5 of the Rule 132 Declaration). Iwasaki et al does not teach or suggest such increased efficiency, and this result is unexpected in view of the teachings of Iwasaki et al.

The Rule 132 Declaration experiments demonstrate that esterification can indeed proceed in an aqueous system due to the unexpected effect of the accelerating reaction at the water interface, created when using compounds in accordance with the claimed invention (see Table 6 of the Rule 132 Declaration). This result is unexpected in view of the teachings of Iwasaki et al.

Iwasaki et al does not teach or suggest that any of the substituents  $R^3$ ,  $R^4$ , and  $R^5$  in the compound can be replaced by a long chain alkyl group in order to form micelles, nor does Iwasaki et al teach or suggest that dehydrating condensation can be performed at a water interface in a micelle system.

Generally speaking, the Rule 132 Declaration experiments show that the condensation reaction is accelerated when all compounds are amphiphilic. Iwasaki et al simply fails to teach or suggest using amphiphilic compounds to make the claimed amphiphilic triazine compound. This is because Iwasaki et al fails to recognize the advantageous formation of a molecular aggregate phase embodied by micelles.

Consequently, the teachings of Iwasaki et al do not render the claims obvious; and even if the Examiner the claims are *prima facie* obvious, the Rule 132 Declaration dequately rebuts any *prima facie* case of obvious.

The Double Patenting Rejection

Claims 6-18 stand rejected under the judicially created doctrine of obviousness-type double patenting over Iwasaki et al (U.S. Patent 6,458,948). The Examiner is respectfully requested to reconsider the propriety of this rejection in view of the Rule 132 Declaration.

Petition for Extension of Time


A request for a three month extension of time is hereby made. Payment is being made through the EFS electronic filing system.

Should the Examiner believe that a telephone interview would be helpful to expedite favorable prosecution, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

In the event any fees are due in connection with the filing of this document, the Commissioner is authorized to charge those fees to our Deposit Account No. 50-1063.

Respectfully submitted,

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